

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
26 July 2001 (26.07.2001)

PCT

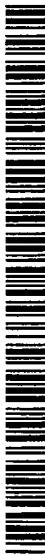
(10) International Publication Number  
**WO 01/52813 A1**

- (51) International Patent Classification<sup>7</sup>: **A61K 9/00**
- (21) International Application Number: **PCT/US01/01925**
- (22) International Filing Date: 19 January 2001 (19.01.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/176,853 19 January 2000 (19.01.2000) US
- (71) Applicant: **PHARMACEUTICAL DISCOVERY CORPORATION [US/US]**; 33 West Main Street, 4th Floor, Elmsford, NY 10523 (US).
- (72) Inventor: **STEINER, Solomon, S.**; 24 Old Wagon Road, Mount Kisco, NY 10549 (US).
- (74) Agents: **PABST, Patrea, L. et al.**; Holland & Knight LLP, One Atlantic Center, Suite 2000, 1201 West Peachtree Street, N.E., Atlanta, GA 30309-3400 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



A1

(54) Title: **MULTI-SPIKE RELEASE FORMULATION FOR DRUG DELIVERY**

(57) Abstract: Methylphenidate or other drugs are provided in a formulation for oral administration that releases the drug in two or more pharmacokinetic spikes, by combining different release forms in a single formulation. In a preferred embodiment for methylphenidate, the first pharmacokinetic spike is achieved by the release of taste-masked methylphenidate which is not enterically coated, while a second pharmacokinetic spike is achieved by the release of methylphenidate in a finely divided form from enterically coated pellets or microparticles formulated for rapid release following dissolution of the enteric coating. A critical aspect of the formulation is the inclusion of excipients that create a burst release following the initial rapid release and uptake. The formulation can be administered as a paste, jelly, suspension, or fast dissolving wafer. To manipulate the dose, the formulation can be provided, for example, as a paste packaged in a tube similar to those used to dispense toothpaste.

**WO 01/52813**

WO 01/52813

PCT/US01/01925

**MULTI-SPIKE RELEASE FORMULATION FOR DRUG DELIVERY****Background Of The Invention**

The present invention is generally in the field of pharmaceutical formulations, and more particularly related to methods and compositions for controlling the pharmacokinetic profile of drugs, such as methylphenidate, which are used in pharmaceutical applications.

This application claims priority to U.S.S.N. 60/176,853 filed January 19, 2000.

Methylphenidate (trade name RITALINT<sup>TM</sup>) is used to treat hyperactivity and attention deficit disorder (ADD) in children. While it is very effective when administered orally, the effects only last for only about three to four hours. It would be desirable to have a dose form that could be administered in the morning and maintain the child throughout the school day. Typical slow release formulations are not suitable because they produce a continuous slow release, approaching a zero order kinetic release profile. Methylphenidate, however, requires a spike or "saw tooth" (i.e. multi-spike) kinetic profile to be effective in the treatment of ADD.

Methylphenidate is currently being used to treat young children who differ widely in their body weight and hence their dose requirement. A desirable formulation would allow for convenient manipulation of dose by the parent. A more accurate dosing regimen could be achieved if it was provided in a formulation that was amenable to apportionment.

Methylphenidate is currently administered in pill form. It is not administered in an aqueous solution since it is so bitter. Young children frequently have difficulty swallowing pills. It would be advantageous to provide methylphenidate in a form that is easily swallowed by children and that masks the unpleasant taste of the drug.

Methylphenidate is known to be abused by individuals who inject it intravenously to achieve a "high". A desirable formulation would be difficult to inject intravenously and hence would reduce the drug's abuse liability.

It is therefore an object of the present invention to provide a

composition for the oral administration of methylphenidate or other drugs that require a multi-spike release.

It is another object of the present invention to provide a composition for the oral administration of methylphenidate or other drugs in an easy to 5 swallow, preferably pleasant tasting, dosage form.

It is a further object of the present invention to provide a composition for oral administration of methylphenidate or other drugs in a form in which the dose of the drug is conveniently manipulated, but which preferably reduces the likelihood of abuse of the drug.

10

### Summary Of The Invention

Methylphenidate or other drugs are provided in a formulation for oral administration that releases the drug in two or more pharmacokinetic spikes, by combining different release forms in a single formulation. In a preferred 15 embodiment for methylphenidate, the first pharmacokinetic spike is achieved by the release of taste-masked methylphenidate which is not enterically coated, while a second pharmacokinetic spike is achieved by the release of methylphenidate in a finely divided form from enterically coated pellets or microparticles formulated for rapid release following dissolution of the 20 enteric coating (i.e., delayed release particles). A critical aspect of the formulation is the inclusion of excipients that create a burst release following the initial rapid release and uptake.

The formulation can be administered as a paste, jelly, suspension, or fast dissolving wafer. The drug can be in the form of drug particles, 25 microencapsulated particles, or drug-polymer particles. In one embodiment, both delayed release and the unprotected methylphenidate are thoroughly mixed and suspended in an appropriate medium to form a paste or a gel. Peanut butter or alginate, flavored with raspberry and a sweetener are examples of the many suitable taste masking agents.

To manipulate the dose, the formulation can be provided, for 30 example, as a paste packaged in a tube similar to those used to dispense toothpaste. The paste can be squeezed out of an orifice of a fixed size such

that a given length of paste contains a specified dose of methylphenidate, e.g., one inch contains 5 mg of methylphenidate, two inches contain 10 mg of methylphenidate. An alternative approach is to package the paste in a hypodermic syringe-like dispenser that is calibrated for dose. Yet another 5 alternative approach is to package the formulation as a gelatinous solid, for example, a jelly candy bar. The bar can be scored or marked in units of methylphenidate for convenient dosing. Furthermore, the potential for intravenous abuse of the methylphenidate is markedly reduced when in the form of a semi-solid suspension of particles in a fat based substrate, such as 10 in peanut butter, or a suspension of solid particles in a semi-solid gel.

#### **Detailed Description Of The Invention**

Formulations have been developed for oral administration to release drug, particularly methylphenidate, in two or more pharmacokinetic spikes, 15 by combining different release forms into a single formulation, where a critical aspect of the formulation is the inclusion of excipients or formulation of the drug to produce immediate release and uptake of the drug after a period of time, typically between two and eight hours, most preferably three house, following the initial delivery and uptake of drug.

20 **I. The Drug Formulation and Methods of Making Them**

A. Drugs to be Delivered

Although essentially any drug suitable for delivery to the gastrointestinal tract can be delivered in the formulation described herein, the preferred drug is one which is beneficially delivered in two or more 25 pharmacokinetic spikes. The preferred drug is methylphenidate (trade name RITALIN<sup>TM</sup>). This drug is available as methylphenidate hydrochloride in tablets of 5, 10 and 20 mg for oral administration. A sustained release formulation is also available. These are administered in divided dosages two or three times daily. The formulations described herein are administered to 30 achieve the same effective dosages, but require only a single administration daily.

B. Release Formulations

The multi-release formulation consists of at least two components: drug which is taken up immediately, and is typically in the form of drug particles, drug solution or drug suspension, without any enteric or controlled release coatings or capsule, and drug that is formulated for delayed release, typically in the form of a capsule, coating, or microparticulate formulation, which delays release and uptake of the drug for a period of hours, typically between two and eight hours, more preferably about three hours. The formulation also includes a means for rapid release of the second delayed release component.

Drug formulations are well known. These can consist of pure drug, either in solution (for immediate uptake), in dry powder form, or in suspension. For the delayed release component, the drug must be in a capsule, a coated tablet, or microparticulate formulation, where the drug is not released until the capsule, coating or microparticulate material is penetrated by hydrolytic and/or enzymatic action. A variety of enteric coatings, protein coatings or films are well known to delay release.

In a preferred embodiment, additional pharmacokinetic spikes are achieved by the release of drug methylphenidate in a finely divided form from enterically coated pellets or microspheres formulated for rapid release following dissolution of the enteric coating. Pellets or microspheres having different types and/or thicknesses of enteric coatings can be combined to yield two, three or more pharmacokinetic spikes.

In a preferred embodiment, the mixture is pelletized into small particles by any one of several methods known to those skilled in the art of pharmaceutics. The pellets are then coated with any one of a number of pH sensitive enteric coating materials, which are water-resistant, by any one of several methods known to those skilled in the art of pharmaceutics.

Rapid release means preferably consist of food or drug grade which react upon exposure to water and/or a defined pH to rapidly generate a burst of gas, for example, carbon dioxide, which "blows apart" the coating, capsule or particulate composition. Typically, these will be a food acid in

dry form (such as citric acid) and a dry powder substance that in combination with water and acid will rapidly form and liberate carbon dioxide (such as baking powder).

This step can be done at the same time as the drug is formed into  
5 pellets or particles. For example, equal weights of methylphenidate, citric acid and sodium bicarbonate are thoroughly mixed with a binding agent, methylcellulose, pelletized into particles having an average diameter of 2 millimeters and placed in a fluidized bed apparatus for coating with EUDRAGIT™. The pellets will produce the second "spike release" of  
10 methylphenidate because the pellets will transit the stomach intact. When the pellets have traveled approximately one third of the length of the small intestines, the pH will have risen sufficiently to dissolve the thin water resistant pH sensitive coating. This takes approximately three to four hours. When water now comes in contact with the citric acid and sodium  
15 bicarbonate, a rapid reaction occurs, releasing carbon dioxide and dispersing the methylphenidate, which because it is rapidly dispersed in a finely divided form, will be rapidly absorbed, yielding the second "pharmacokinetic spike".

#### C. Carriers

The formulation can also contain binders, taste modifying  
20 components, food colorings, and viscosity modifying agents. The drug formulation may be in the form of a suspension, capsule, tablet, paste, gel, or solid or semi-solid form such as a "candy bar". The advantages of the suspension, paste, gel, and solid or semi-solid formulations is that they are readily divided into dosages which can be made more exact based on the age  
25 and size of the recipient, and are also more difficult to abuse since they are not injectable.

Taste modifying materials are well known. Bubble gum and fruit flavorings are commonly used for pediatric formulations. For example the drug can be dissolved or suspended in an aqueous solution containing  
30 sweeteners and/or flavoring agents, which are well known in the art. Peanut butter or alginate, flavored with raspberry and a sweetener are examples of the many mediums suitable as taste masking agents.

Binding agents may also be added if necessary or desirable. For example, the formulation can be administered orally as a paste, jelly, suspension, or fast dissolving wafer. In one embodiment, both the pelletized and the unprotected methylphenidate are thoroughly mixed and suspended in 5 an appropriate medium to form a paste or a gel.

In a preferred embodiment for methylphenidate, the first pharmacokinetic spike is achieved by the release of taste-masked methylphenidate which is not enterically coated, while a second pharmacokinetic spike is achieved by the release of methylphenidate in a 10 finely divided form from enterically coated pellets or microparticles formulated for rapid release following dissolution of the enteric coating.

## II. Methods of Administration and Dosage Manipulation

To manipulate the dose, the formulation can be provided, for example, as a paste packaged in a tube similar to those used to dispense 15 toothpaste. The paste can be squeezed out of an orifice of a fixed size such that a given length of paste contains a specified dose of methylphenidate, e.g., one inch contains 5 mg of methylphenidate, two inches contain 10 mg of methylphenidate.

An alternative approach is to package the paste in a hypodermic 20 syringe-like dispenser that is calibrated for dose. Yet another alternative approach is to package the formulation as a gelatinous solid, for example, a jelly candy bar. The bar can be scored or marked in units of methylphenidate for convenient dosing.

I claim:

1. A composition for the oral administration of a drug to a patient comprising

a first component in a form releasing a first dose of the drug immediately following ingestion of the composition; and

a second component in a form rapidly releasing a second dose of the drug at a second time after release of the first dose,

wherein the first and second doses provide a multi-spike pharmacokinetic profile of the drug and wherein the rapid release is achieved through the use of reagents that immediately disperse or expose the second dose of the drug so that it can be absorbed through the gastrointestinal tract.
2. The composition of claim 1 wherein the drug is methylphenidate.
3. The composition of claim 1 comprising taste masking materials.
4. The composition of claim 1 wherein the drug of the second component is enteric coated and rapidly released in a finely divided form following dissolution of the enteric coating.
5. The composition of claim 1 wherein the second component is in the form of pellets or microspheres comprising an acid and a dry powder, wherein the dry powder and acid, upon contact with water, will form and liberate carbon dioxide.
6. The composition of claim 5 wherein the acid is a food acid and the dry powder is baking powder.
7. The composition of claim 5 comprising a binding agent wherein the composition is in the form of a solid or semi-solid food or candy.
8. The composition of claim 1 in the form of a paste, jelly, suspension, or fast-dissolving wafer.
9. The composition of claim 1 in the form of a gelatinous solid.

10. A drug dosage dispenser comprising  
a composition for the oral administration of a drug to a patient  
comprising  
    a first component in a form releasing a first dose of the drug  
immediately following ingestion of the composition; and  
    a second component in a form rapidly releasing a second dose of the  
drug at a second time after release of the first dose,  
        wherein the first and second doses provide a multi-spike  
pharmacokinetic profile of the drug and wherein the rapid release is achieved  
through the use of reagents that immediately disperse or expose the second  
dose of the drug so that it can be absorbed through the gastrointestinal tract,  
        wherein the composition is in the form of a paste or gel, and  
        a compressible device for dispensing a measured dose of the  
composition.
11. A method of administering a drug to a patient in need thereof,  
comprising orally administering a composition that comprises  
    a first component in a form releasing a first dose of the drug  
immediately following ingestion of the composition; and  
    a second component in a form rapidly releasing a second dose of the  
drug at a second time after release of the first dose,  
        wherein the first and second doses provide a multi-spike  
pharmacokinetic profile of the drug and wherein the rapid release is achieved  
through the use of reagents that immediately disperse or expose the second  
dose of the drug so that it can be absorbed through the gastrointestinal tract.
12. The method of claim 11 wherein the drug is methylphenidate
13. The method of claim 12 wherein the second dose is released after  
two to eight hours following release of the first dose.
14. The method of claim 11 wherein the composition is in the form  
of a paste or gel, and is administered using a compressible device for  
dispensing a measured dose of the composition.

15. The method of claim 11 wherein the composition is in the form of a solid or semi-solid which can be apportioned to provide the correct dosage form, and is apportioned at the time of administration to an individual in need of treatment thereof.

16. The method of claim 11 wherein the second component is in the form of pellets or microspheres comprising an acid and a dry powder, wherein the dry powder and acid, upon contact with water, will form and liberate carbon dioxide.

17. The method of claim 16 wherein the acid is a food acid and the dry powder is baking powder.

18. The method of claim 11 wherein the composition is in the form of a solid or semi-solid food or candy.

19. The method of claim 11 wherein the composition is administered in the form of a paste, jelly, suspension, or fast-dissolving wafer.

20. The method of claim 11 wherein the composition is administered in the form of a gelatinous solid.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 01/01925

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 03471 A (MEHTA ATUL M ;DARIANI MAGHSOUD M (US); ZEITLIN ANDREW L (US)) 28 January 1999 (1999-01-28) the whole document ----- RICCHI E. ET AL: "Development of a double pulse release methylphenidate HCl formulation." PROCEEDINGS OF THE CONTROLLED RELEASE SOCIETY, vol. 26, June 1999 (1999-06), pages 945-946, XP002166934 abstract -----	1-3, 11-13
X	----- WO 00 35426 A (KRISHNAMURTHY THINNAYAM N ;DARKE ANDREW (CA); EURO CELTIQUE SA (LU)) 22 June 2000 (2000-06-22) the whole document -----	1-3, 11-13
P, X	-----	1-4, 11-13

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

9 May 2001

01/06/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Marttin, E

**INTERNATIONAL SEARCH REPORT**

Intern	Al Application No
PCT/US 01/01925	

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 00 25752 A (FANNING NIALL M M ;DEVANE JOHN G (IE); ELAN CORP PLC (IE); STARK P) 11 May 2000 (2000-05-11) the whole document ----	1-4, 11-13
P, X	WO 00 59479 A (CHUNGI SHUBHA ;MIDHA KAMAL K (US); PHARMAQUEST LTD (US); IORIO THE) 12 October 2000 (2000-10-12) the whole document ----	1-3, 11-13
A	US 5 178 878 A (WEHLING FRED ET AL) 12 January 1993 (1993-01-12) column 2, line 18 - line 51 column 2, line 66 -column 3, line 39 column 5, line 57 -column 6, line 17 column 11, line 56 -column 12, line 20; claims; example 1 ----	1,5,6, 16,17
A	EP 0 379 147 A (STERLING DRUG INC) 25 July 1990 (1990-07-25) page 1, line 1 - line 2 page 1, line 27 - line 32 page 3, line 29 - line 36; claim 1 ----	1,8,10, 14,15,19
A	KIMKO H C ET AL: "PHARMACOKINETICS AND CLINICAL EFFECTIVENESS OF METHYLPHENIDATE" CLINICAL PHARMACOKINETICS, ADIES INTERNATIONAL, PARIS, FR, vol. 37, no. 6, December 1999 (1999-12), pages 457-470, XP000950000 ISSN: 0312-5963 page 458, line 4 - line 10 page 462, right-hand column, last paragraph -page 463, left-hand column, paragraph 1 -----	1-20

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-20 relate to a composition defined by reference to a desirable characteristic or property, namely "a first component in a form releasing a first dose of the drug immediately following ingestion of the composition; and a second component in a form rapidly releasing a second dose of the drug at a second time after release of the first dose, wherein the first and second doses provide a multi-spike pharmacokinetic profile of a drug", lacking any technical feature allowing a search for these compositions and lacking an essential technical feature which is the presence of methylphenidate (see the description and claim 2). The term "a first component in a form releasing a first dose of the drug immediately following ingestion of the composition; and a second component in a form rapidly releasing a second dose of the drug at a second time after release of the first dose, wherein the first and second doses provide a multi-spike pharmacokinetic profile of a drug" defines the composition by its pharmacokinetic profile. However, a composition cannot be sufficiently characterised by its pharmacokinetic profile as is done by an expression like "a first component in a form releasing a first dose of the drug immediately following ingestion of the composition; and a second component in a form rapidly releasing a second dose of the drug at a second time after release of the first dose, wherein the first and second doses provide a multi-spike pharmacokinetic profile of a drug", because it is impossible to know which compositions are encompassed in this expression.

The claims cover all compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for the concept of a first component in a form releasing a first dose of the drug immediately following ingestion of the composition; and a second component in a form rapidly releasing a second dose of the drug at a second time after release of the first dose, wherein the first and second doses provide a multi-spike pharmacokinetic profile of a drug, and for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to what is an essential feature of the invention, namely the inclusion of the drug methylphenidate in the composition as mentioned in the description and in claims 2 and 12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No
PCT/US 01/01925

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9903471	A 28-01-1999	US 5837284 A AU 7834398 A DE 1001772 T EP 1001772 A ES 2153338 T		17-11-1998 10-02-1999 01-03-2001 24-05-2000 01-03-2001
WO 0035426	A 22-06-2000	AU 2122700 A		03-07-2000
WO 0025752	A 11-05-2000	AU 1335000 A		22-05-2000
WO 0059479	A 12-10-2000	AU 4221300 A AU 4334700 A WO 0059481 A		23-10-2000 23-10-2000 12-10-2000
US 5178878	A 12-01-1993	CA 2061917 A,C AU 646232 B AU 6601290 A EP 0494972 A JP 5500956 T WO 9104757 A US 5223264 A AT 145551 T DE 69029273 D DE 69029273 T DK 494972 T EP 0737473 A ES 2097155 T		27-08-1993 17-02-1994 28-04-1991 22-07-1992 25-02-1993 18-04-1991 29-06-1993 15-12-1996 09-01-1997 12-06-1997 12-05-1997 16-10-1996 01-04-1997
EP 0379147	A 25-07-1990	US 5288479 A AU 622259 B AU 4786090 A CA 2007752 A DE 69012842 D DE 69012842 T DK 379147 T FI 900099 A IE 64163 B JP 2247116 A JP 2879917 B KR 149494 B NO 180282 B NZ 232025 A		22-02-1994 02-04-1992 26-07-1990 17-07-1990 03-11-1994 20-04-1995 12-12-1994 18-07-1990 12-07-1995 02-10-1990 05-04-1999 15-10-1998 16-12-1996 26-07-1991